# Imperfect vaccines and the evolution of pathogens causing acute infections in vertebrates

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Supplementary Materials

February 21, 2006

## The optimal growth rate, total transmission, and duration of infection in the absence of heterogeneity

In unvaccinated and anti-growth vaccinated hosts, we assume no anti-transmission immune response $X_2$. Then by dividing eq. (2) by eq. (3) and integrating we obtain (for more detail see Ganusov et al. (2002)):

$$\ln\left(\frac{P(t)+k}{P_0+k}\right) = \frac{r}{s}\ln\left(\frac{X_1(t)}{X_{10}}\right) - \frac{h_1}{s}(X_1(t)-X_{10}). \tag{14}$$

Noting that the maximal transmission occurs when $P(t)$ approaches the lethal density $D$, we set $dP(t)/dt\ |_{t=t_{peak}} = 0$ and obtain $X_1(t_{peak}) = r/h_1$. Since the maximal transmission occurs at $r = r^*$, we obtain eq. (6) using eq. (14) with $t = t_{peak}$ at the limits $P_0 \ll k$, $D \gg k$ and $h_1 X_{10}/s \ll 1$ (Antia et al. 1994). For a linear transmissibility $\zeta[P(t)]$, the total transmission of pathogens not killing the host (with $r \leq r^*$) is

$$l(r) = c\int_0^\infty P(t)dt = c\int_0^\infty \frac{P(t)+k}{sX_1(t)}\dot{X}_1 dt \approx \frac{kc}{s}\left(\frac{s}{h_1 X_{10}}\right)^{r/s}\Gamma(r/s), \tag{15}$$

where we assumed a large expansion of immune cells ($h_1 X_1(\infty)/s \gg 1$ and $\Gamma(x)$ is the Euler gamma function) and also used the relationship between $P(t)$ and $X_1(t)$ given in eq. (14).

When $r \gg r^*$, we assume that the pathogen population grows exponentially until it kills the host; then the total transmission is

$$l(r) = c\frac{D}{r}. \tag{16}$$

We calculate the duration of acute infection for the cases when $r < r^*$ and $r > r^*$ separately ($r^*$ is given in eq. (6)). If $r > r^*$ the pathogen kills the host; approximating that the pathogen population grows exponentially until it kills the host, the duration of acute infection $\Delta(r)$ will be:

$$\Delta(r) \approx \frac{\ln(D/P_0)}{r}. \tag{17}$$

When $r < r^*$ the pathogen is cleared by the immune response; the duration of acute infection is found by integrating eq. (3):

$$\Delta(r) = \int_{X_{10}}^{X_1(\infty)} \frac{dx}{sx}\left(1 - \frac{k}{P_0+k}\left(\frac{X_{10}}{x}\right)^{r/s} e^{h_1(x-X_{10})/s}\right)^{-1}, \tag{18}$$

where the maximum density of immune cells $X_1(\infty)$ is approximately a solution of the equation: $r\ln(X_1(\infty)/X_{10}) = h_1(X_1(\infty) - X_{10})$ obtained from eq. (14) by setting $P(\infty) = 0$.

In anti-transmission vaccinated hosts, assuming that the anti-transmission immune response expands moderately (i.e, $h_2X_2(\infty) \ll 1$), we obtain similar expressions for $r^*$, $l(r)$ at $r \gg r^*$, and $\Delta(r)$. However, the total transmission $l(r)$ at $r \le r^*$ is changed:

$$\begin{aligned} l(r) &= c\int_0^\infty \frac{P(t)}{1+h_2X_2(t)}dt \approx \frac{kc}{s}\left(\frac{s}{h_1X_{10}}\right)^{r/s}\int_0^\infty \frac{x^{r/s-1}e^{-x}}{1+xh_2X_{20}/(sh_1X_{10})}dx = \\ &= \frac{kc}{s}\left(\frac{s^2}{h_2X_{20}}\right)^{r/s} e^{\frac{sh_1X_{10}}{h_2X_{20}}}\Gamma\left(\frac{r}{s}\right)\Gamma\left(1-\frac{r}{s}, \frac{sh_1X_{10}}{h_2X_{20}}\right), \end{aligned} \tag{19}$$

where $\Gamma(n,z)$ is an incomplete gamma function. We used the following relationship between the two responses: $X_2(t)/X_1(t) = X_{20}/X_{10}$, obtained by integrating eq.(3) and (10), and other approximations as before. We have verified that the approximation given in eq. (19) is valid for the description of the total transmission of

pathogens in vaccinated hosts for parameters used in the main text. To plot the total transmission of pathogens with different growth rates in the absence of heterogeneity we use eqn. (4) or (11) with $P(t)$ and $X_2(t)$ found by direct integration of eqns. (2), (3), and (10).

## The average total transmission and virulence of pathogens in a heterogeneous population

The average total transmission of pathogens in a heterogeneous population given by eq. (8) can be calculated using the above approximations for $l(r)$:

$$L(r) \approx \int_0^{r^*} l(r')f(r',r)dr' + c\int_{r^*}^{\infty}\frac{D}{r'}f(r',r)\,dr', \tag{20}$$

with $l(r')$ given in eq. (19) and $r^*$ calculated in accord with eqn. (6) at a known precursor number $X_{10}$. This approximation was used to calculate the average total transmission and to generate predictions shown in the main text.

The case mortality is the probability of host's death following the infection. In a host population with heterogeneity defined by $f(r',r)$, an infection will result in host's death if the current growth rate $r'$ is greater than $r^*$:

$$m(r') = \begin{cases} 1, \text{ if } r' > r^*, \\ 0, \text{ otherwise.} \end{cases} \tag{21}$$

Integrating $m(r')$ over all growth rates, we obtain the average case mortality $M(r)$ given in eq. (9). In Figure 9 we show an example of the average total transmission $L(r)$ and virulence of pathogens $M(r)$ with different growth rates in vaccinated and unvaccinated hosts.

## Epidemiological trade-offs

We have shown previously that using models of the within-host dynamics of pathogens one can estimate the parameters determining the rate of epidemiological spread of the pathogen-induced disease such as transmissibility $\beta$, host recovery rate $\nu$, host

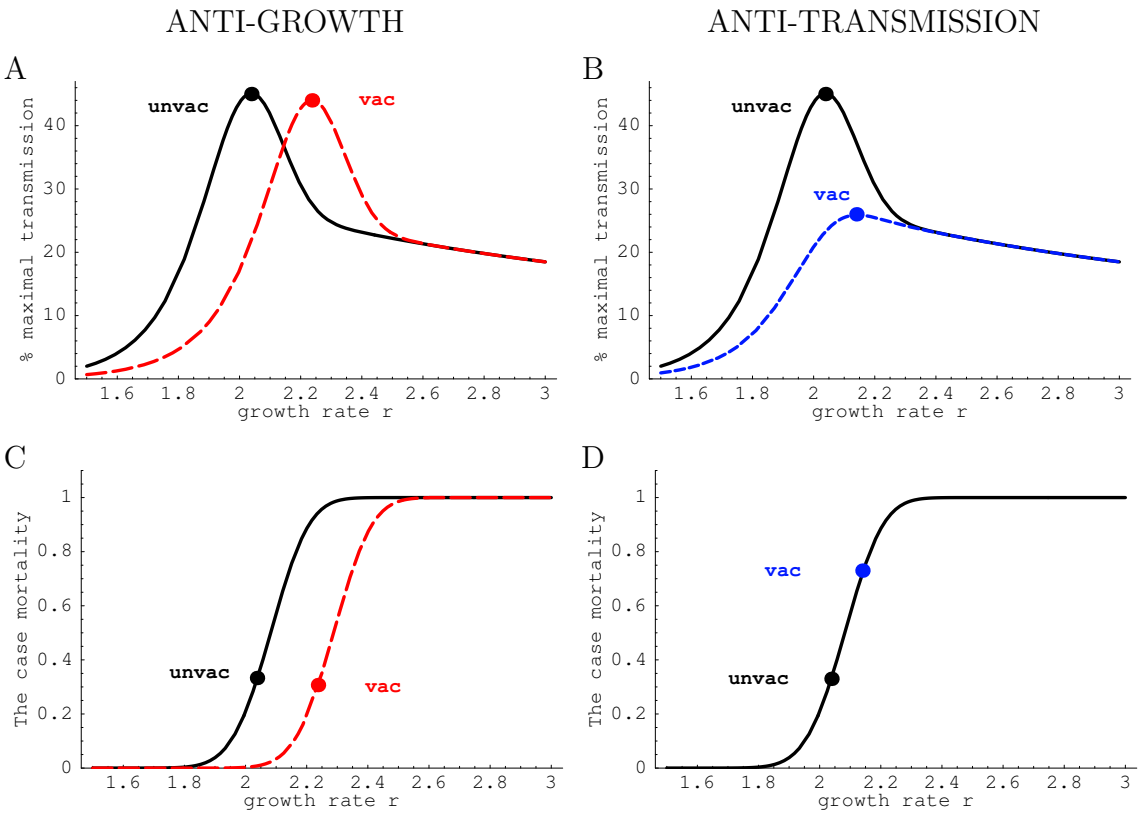


**Figure 9:** The average total transmission $L(r)$ (panels A and B) and virulence (panels C and D) of pathogens with different growth rates in unvaccinated (solid lines), anti-growth (long-dashed lines, left panels) and anti-transmission (short-dashed lines, right panels) vaccinated hosts in the presence of heterogeneity. The average total transmissions are normalized to the maximum total transmission in unvaccinated hosts in the absence of heterogeneity. Dots denote ES pathogen characteristics. Parameters are the same as in the main text and $\sigma = 0.1$.

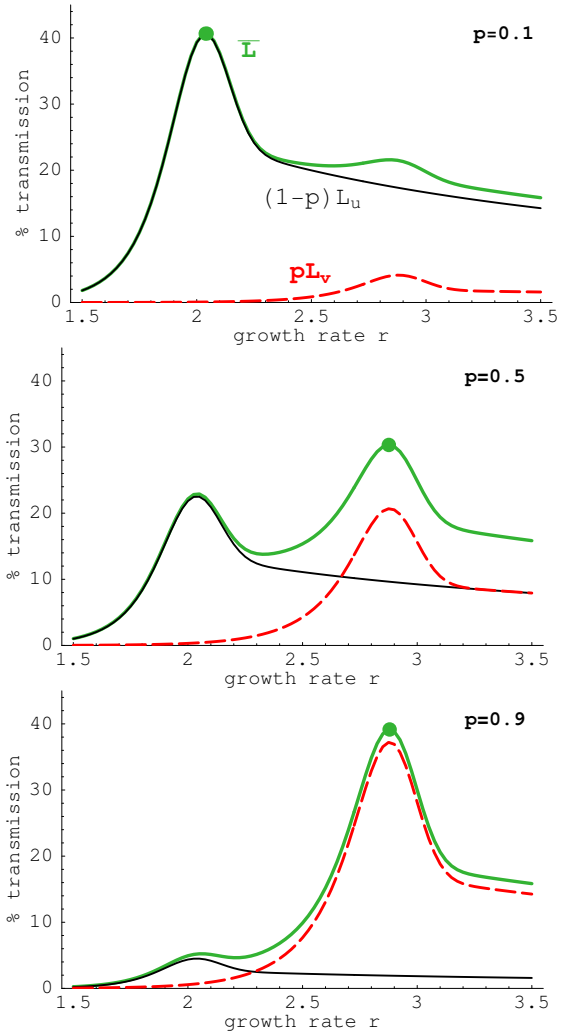


**Figure 10:** Changes in the total transmission of pathogens with different growth rates occurring with the increasing fraction of anti-growth vaccinated hosts $p$ at high vaccine efficacy (i.e., when precursor number of anti-growth immune response is increased 10 fold after vaccination). Thin continuous lines denote the total transmission of pathogens from unvaccinated hosts, $(1-p)L_u(r)$. Dashed lines denotes the total transmission of pathogens from anti-growth vaccinated hosts, $pL_v(r)$. Bold continuous lines denote the total transmission of pathogens from the whole population $\overline{L}(r) = pL_v(r) + (1-p)L_u(r)$. The dot denotes the ES total transmission. All total transmissions are normalized to the ES pathogen transmission in unvaccinated hosts in the absence of heterogeneity. The fraction of vaccinated hosts $p$ is marked. Parameters are the same as in the main text. Note that there are two maxima in the total transmission, and at some intermediate coverage $0.1 < p < 0.5$ the pathogen switches from one maximum to another.

mortality rate $\alpha$ and the basic reproductive number $R_0$ (Ganusov et al. 2002). The epidemiological parameters can be estimated as follows.

First, the basic reproductive number, $R_0$, is proportional to the average number of pathogens transmitted from an infected host over the course of acute infection, i.e. $R_0(r) = uL(r)$, where $u$ is a constant. Second, the transmission rate of a pathogen with the growth rate $r$, $\hat{\beta}(r)$, equals the total transmission of the pathogen over the course of acute infection, $l(r)$, divided by the duration of acute infection, $\Delta(r)$:

$$\hat{\beta}(r) = u\frac{l(r)}{\Delta(r)}. \tag{22}$$

The average transmissibility of the pathogen in a heterogeneous population, $\beta(r)$, with heterogeneity described by $f(r', r)$ is:

$$\beta(r) = \int_0^\infty \hat{\beta}(r')f(r', r)\, dr' = u\int_0^\infty \frac{l(r')}{\Delta(r')}f(r', r)\, dr'. \tag{23}$$

The average host mortality rate $\alpha(r)$ and host recovery rate $\nu(r)$ are calculated in a similar way:

$$\alpha(r) = \int_0^\infty \frac{m(r')}{\Delta(r')}f(r', r)\, dr', \tag{24}$$

$$\nu(r) = \int_0^\infty \frac{1 - m(r')}{\Delta(r')}f(r', r)\, dr'. \tag{25}$$

Now, by estimating parameters $\beta$, $\nu$, $\alpha$ and $R_0$ for a pathogen with a given growth rate $r$, one can infer the correlations (trade-offs) between these pathogen characteristics.

## Explicit modeling of two stages of the pathogen's life cycle

In the main text we have focused on the analysis of a simple model that involves one pathogen population and two immune response, directed against pathogen's growth and transmission. Here we shortly describe a more general model, that explicitly describes the dynamics of two stages in the pathogen life-cycle: replicating $P_1$ and terminally-differentiated transmitting $P_2$ (Figure 11). We assume that the

infection is initiated by the replicating stage, starting from a small inoculum $P_{10}$. We also assume that the conversion rate $\lambda$ from the replicating to transmitting stage is constant during the infection and cannot evolve (for a more general case, see (Koella and Antia 1996)). Two pathogen populations are controlled by different immune responses, $X_1$ and $X_2$, expanding for $X_{10}$ and $X_{20}$ precursors, respectively, and killing the pathogens at the per capita rates $h_1$ and $h_2$, respectively.

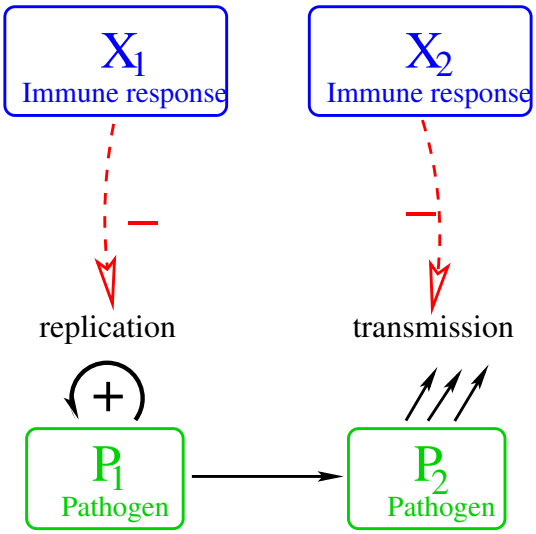


**Figure 11:** The cartoon of interactions between the pathogen and host's immune responses when a separate transmission stage is modeled. We assume that pathogen population $P_1$ replicates exponentially and with a probability $\lambda$ differentiates into non-replicating transmission stage $P_2$. See Figure 2 and eqn. (26)–(29) for other detail.

Then the dynamics of pathogens and immune responses are given by the equations:

$$\frac{dP_1}{dt} = r(1-2\lambda)P_1 - h_1X_1P_1, \quad (26)$$

$$\frac{dP_2}{dt} = r\lambda P_1 - h_2X_2P_2, \quad (27)$$

$$\frac{dX_1}{dt} = \frac{sX_1P_1}{k_1+P_1}, \quad (28)$$

$$\frac{dX_2}{dt} = \frac{sX_2P_2}{k_2+P_2}, \quad (29)$$

with other parameters similar to those in the simple model given in eqn. (2)–(3). Since the conversion probability is small, $\lambda \ll 1$, (Koella and Antia 1996; Taylor

and Read 1997), we assume that the pathogen kills the host when the replicating stage $P_1$ reaches the lethal density $D$ and that there is no transmission from a dead host. The rate of pathogen transmission from infected hosts, $\zeta$, to be proportional to the within-host density of the transmission stage, $P_2$, $\zeta[P_2(t)] = cP_2(t)$. The total transmission $l(r)$ of the pathogen with the growth rate $r$ during acute infection of duration $\Delta$ then is

$$l(r) = \int_0^\Delta \zeta[P_2(t)]\,dt = c\int_0^\Delta P_2(t)\,dt. \tag{30}$$

In Figure 12 we plot the dynamics of the infection and the total transmission $l(r)$ for pathogens with different growth rates in vaccinated and unvaccinated hosts. As in the main text we assume that vaccination increases the precursor number of the corresponding immune response. Importantly, since both responses are present in unvaccinated and vaccinated hosts, we cannot exclude the competition between the responses for the pathogen required for the immune responses' expansion. This in turn affects the changes in the maximal total transmission occurring with vaccination (see below).

In this more complex model we find that in unvaccinated hosts the replicating stage falls short of the lethal density, and the pathogen obtains high total transmission (set to be 100%). In anti-growth vaccinated hosts ($X_{10} = 2$, Figure 12B) replicating stage reaches lower densities leading to lower densities of the transmission stage, in turn leading to a decreased total transmission ($l \approx 30\%$). Importantly, however, the ES pathogen total transmission in vaccinated hosts is higher than the ES transmission in unvaccinated hosts (Figure 12D). This occurs because while in both cases pathogen densities are similar, the infection is of a shorter duration in vaccinated hosts leading to a lower density for the anti-transmission immune response $X_2$ which in turn results in lower inhibition of pathogen transmission (Figure 12D). Similarly to the simple model, analyzed in the main text, the dynamics of the replication stage do not change after anti-transmission vaccination, but the ES pathogen transmission is reduced. These results are qualitatively similar to the results of the simple model (compare Figures 4 and 12) with the exception of an increased maximal total transmission in anti-growth vaccinated hosts. We thus expect qualitatively similar changes in virulence of pathogens evolving in a partially-vaccinated host population.

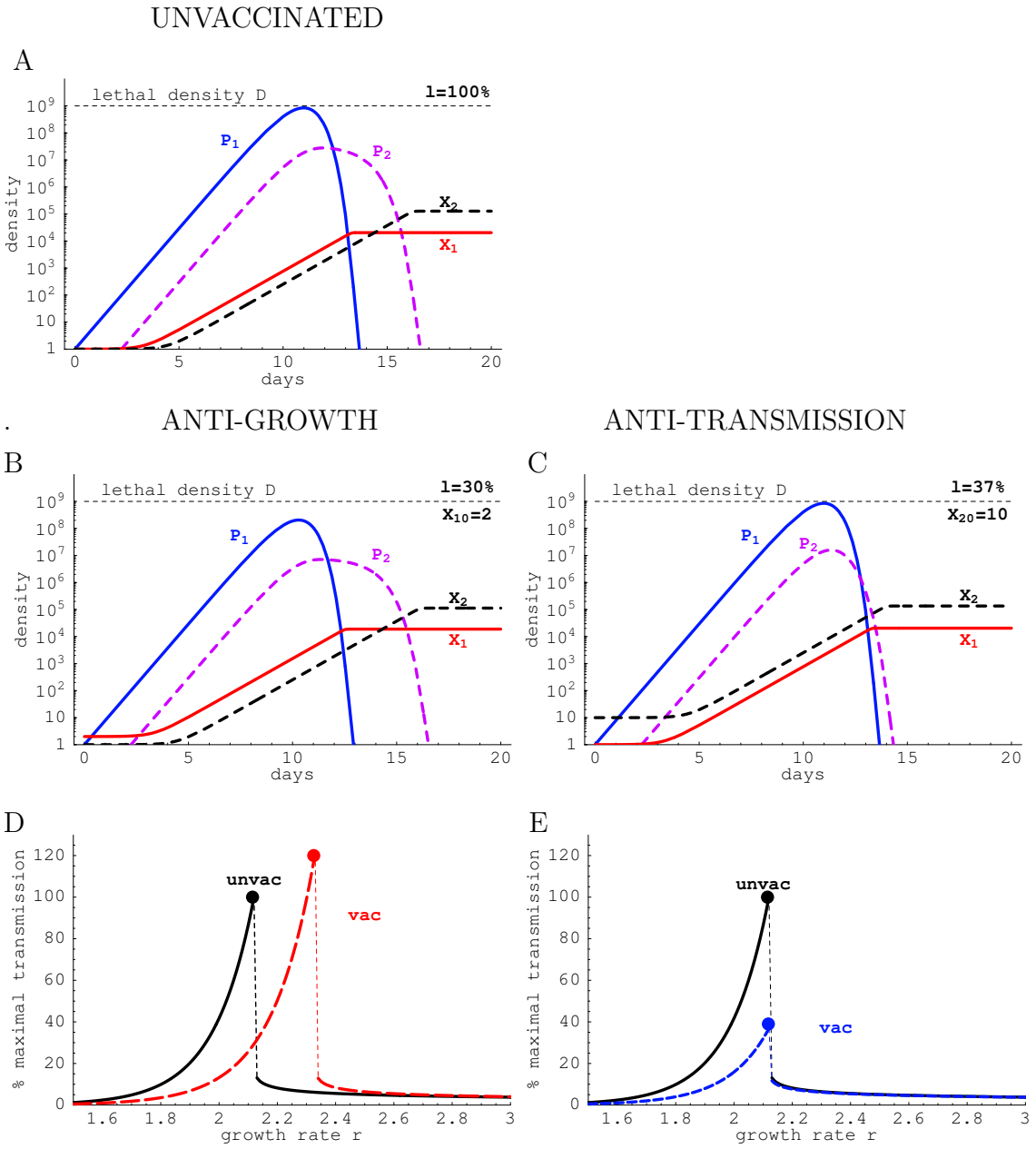


**Figure 12:** Within-host dynamics of pathogens and the host's immune responses and the pathogen's total transmission in unvaccinated hosts ($X_{10} = X_{20} = 1$, panel A), in anti-growth vaccinated hosts ($X_{10} = 2$, panels B and D) and anti-transmission vaccinated hosts ($X_{20} = 10$, panels C and E). Parameters are $P_1(0) = 1$, $P_2(0) = 0$, $k_2 = 10^2$, $r = 2.1$, $\lambda = 0.01$; other parameters are the same as in the main text.

# References

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